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REMARKS

Claims 1-6, 22, 25, and 34 remain in prosecution, and stand ready for action on the merits. Reexamination and reconsideration of the present application in view of the amendments and remarks presented herein are respectfully requested.

Amendments

Claims 7-21, 23-24, 26-33, and 35-55 are withdrawn to make the claims conform to the restriction and election.

Election/Restrictions under 35 U.S.C. § 121

1. Restriction

The Office Action made the following restriction:

I. Claims 1-34, drawn to a therapeutic combination comprising a COX-2 inhibitor compound source and a steroid compound, classified in Class 514, subclass 406, 473, 171, 177, 178, for example.

II. Claims 35-55, drawn to a method of treating dysmenorrhea in a patient employing a therapeutic combination comprising a COX-2 inhibitor compound source and a steroid compound, classified in class 514, subclass 406, 473, 171, 177, 178, for example.

2. Election

The Applicant elects Group I without traverse and without prejudice to the non-elected claims.

Steroid Compound Species Election

1. Requirement of the Office Action for Election of a Steroid Compound

The Office Action, citing MPEP § 803.02, makes a requirement to provisionally elect a single species since, according to the Office Action, the species of steroid compounds described in the present application are independent and patentably distinct.

2. Election of a Steroid Compound

The Applicant provisionally elects ethinyl estradiol as the steroid compound species. This election is made without traverse and without prejudice to the other steroid compound species described in the present application.

COX-2 Inhibitor Species Election

1. Requirement of the Office Action for Election of a COX-2 Inhibitor

The Office Action, citing MPEP § 803.02, makes a requirement to provisionally elect a single species since, according to the Office Action, the species of COX-2 inhibitors described in the present application independent and patentably distinct.

2. Election of a COX-2 Inhibitor

The Applicant provisionally elects celecoxib as the COX-2 inhibitor species. This election is made without traverse and without prejudice to the other steroid compound species described in the present application.

Rejection of Claims 1 and 22 Under 35 U.S.C. § 102(b)

Claims 1 and 22 stand rejected under 35 U.S.C. § 102(b) as being unpatentable over Deligeorglou (Ann. NY Acad. Sci, 900, 237-244 (2000)). Insofar as this rejection may apply to claims 1 and 22, it is traversed. Reconsideration and withdrawal thereof are requested.

Deligeorglou states on page 241 that following treatment for dysmenorrhea by administration of oral contraceptives, "If there is not good relief of the dysmenorrhea, prostaglandin synthetase inhibitor can be added." Deligeorglou cites a 1982 reference (P.E. Alvin et al., Pediatrics, 70, 131-149 (1982)) as authority for this statement.

However, the existence of COX-2 was not elucidated until the late 1980's. (See, for example, A. Raz et al., Advances in Prostaglandin, Thromboxane, and Leukotriene Research, 20, 22-27 (1990), a copy of which is attached to this response for convenience. Attention is drawn, for example to the first full paragraph, last sentence, on page 24 of that reference.)

Furthermore, the first drug which was demonstrated to be COX-2 specific in humans, celecoxib, was not commercialized until 1999. (See, for example, J. Wallace et al., Curr. Opin. Anti-Inflammatory Immunomodulatory Invest. Drugs, 1(2) 100-110 (1999), a copy of which is attached to this response for convenience.)

The Deligeorglou reference therefore does not disclose in a single prior art reference each element of the claims under consideration. Therefore, Deligeorglou does not anticipate the present invention. (See, for example, W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ 303, 313 (Fed. Cir. 1983).)

The Applicant believes that Claims 1 and 22 stand allowable.

Rejection of Claims 1-6, 22, 25, and 34 under 35 U.S.C. § 103(a)

1. Office Action Rejection

The Office Action rejects Claims 1-6, 22, 25, and 34 under 35 U.S.C. § 103(a) as unpatentable over Deligeorglou in view of PDR (50th Ed., 1996) and Harrison et al. (US Patent No. 6,086,909). The Office Action (citing In re Kerkhoven, 205 USPQ 1069 (Fed. Cir. 1980)) states that "combining two agents which are known to be useful to treat dysmenorrhea individually into a single composition useful for the very same purpose is *prima facie* obvious.

2. The Present Claims Are Not Prima Facie Obvious

The Applicants contend that a case of *prima facie* obviousness has not been established. "To establish a *prima facie* case of obviousness . . . the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." (MPEP § 2142).

The Federal Circuit stated in In re Geiger (2 USPQ2d 1277, 1278 (Fed. Cir. 1987)), "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching suggestion or incentive supporting the combination." In that case appellants claimed a method of inhibiting scale formation on and corrosion of metallic parts in cooling water systems by use of compositions containing (1) a sulfonated styrene/maleic anhydride copolymer, (2) a water soluble zinc compound, and (3) an organo-phosphorus acid

compound or water soluble salt thereof. Each of these components were individually known in the art at the time the patent application was filed to inhibit corrosion in cooling water systems. The Federal Circuit concluded that appellant's claims were not *prima facie* obvious: "At best, in view of these disclosures [in the art], one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 U.S.C. § 103."

Applying this law to the present case, even if, as the Office Action asserts, the individual components are known individually in the art to be useful for the treatment of dysmenorrhea, this information alone does not establish *prima facie* obviousness.

The Applicants believe Claims 1-6, 22, 25, and 34 stand allowable.

Applicant respectfully requests reconsideration of all the standing claims and further requests early favorable action by the Examiner.

If the Examiner believes a telephonic interview with Applicant's representative would aid in the prosecution of this application, he is cordially invited to contact Applicant's representative at the below listed number.

Respectfully submitted,

Date: April 22, 2003

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REGULATION OF PROSTANOIDS SYNTHESIS IN HUMAN FIBROBLASTS AND HUMAN BLOOD MONOCYTES BY INTERLEUKIN-1, ENDOTOXIN, AND GLUCOCORTICOIDS

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Modulation of prostaglandin production occurs either at the release of arachidonic acid from cellular phospholipids or during the cyclooxygenase-mediated conversion of arachidonate into prostaglandins. The Mϕ-derived monokine interleukin-1 (IL-1) stimulates formation of PGE_2 in fibroblasts (1,2) as well as formation of PGE_2 and other cyclooxygenase (COX) products in other cells. Fibroblast-produced PGE_2 may in turn feedback suppress Mϕ release of IL-1 (3-5) as well as Mϕ immune competency as judged by Ia antigen expression (6). Studies with human synovial cells (7) and rabbit chondrocytes (8) have indicated that IL-1 induced PGE_2 production is mediated via stimulation of phospholipase(s). Our studies with human dermal fibroblasts (9) have demonstrated that monocyte-conditioned media (which contains IL-1) produced increased V_{max} of COX that appeared to be dependent on new protein synthesis.

We employed a polyclonal antisera against sheep COX that cross-reacted with the human COX and permitted the selective and quantitative immunoprecipitation of [^{35}S]methionine COX from fibroblast cell sonicates, thus enabling us to quantitate changes in the turnover of COX (1).

Effect of IL-1 on Fibroblast Cyclooxygenase - The time-dependent IL-1 induction of fibroblast PGE_2 production and of new cyclooxygenase enzyme synthesis was assessed by assaying in parallel three different parameters: (a) PGE_2 released into the media; (b) cellular COX activity in the solubilized cell sonicate; and (c) the radioactivity in the COX band following [^{35}S]methionine labeling, immunoprecipitation, and SDS-PAGE electrophoresis. Within 6 hr of IL-1 addition, there is a 3-fold increase in the rate of COX synthesized as indicated by the increased [^{35}S]methionine incorporation into the COX band and parallel stimulation of COX activity. As little as 0.03 unit/ml of Il-1 caused significant stimulation of COX synthesis, half-maximal stimulation being at approximately 0.1 unit/ml, with maximal stimulation at 0.3 unit/ml (1). To estimate the COX turnover, cells preincubated with IL-1 for 16 hrs, were then labeled with [^{35}S]methionine for varying periods after which they were processed for immunoprecipitation and SDS-PAGE electrophoresis. Synthesis of [^{35}S]methionine COX increased gradually during 3 hr of labeling and was maximal at 6 hr (1). A theoretical half-life of 1 hr would yield 87.5% of maximal steady state labeling level after 3 hr (i.e., 3 half-lives). Contrasting this with the observed 85% of the maximal, steady state radioactivity after a three hour labeling period indicates that the half-life of fibroblast cyclooxygenase is approximately 1 hr. This conclusion is supported by our results from pulse-chase experiments (1).

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TABLE 1. Effect of mRNA and protein synthesis inhibitors on IL-1 stimulation of fibroblasts cyclooxygenase activity

Addition during first incubation (0-4 hrs)	Addition during second incubation (4-8 hrs)	COX activity pg $PGE_2/\mu g$ protein/min (n=4)
(control)	- -	4.5 ± 0.4
IL-1 (0.3 unit/ml)	- -	29.6 ± 2.3*
IL-1	actinomycin D (1μM)	34.4 ± 4.5*
IL-1	cycloheximide (10 μM)	3.0 ± 0.6
IL-1 + actin. D	- -	2.4 ± 0.4

* Significantly different from control ($p<0.01$, t-test).

We next attempted to resolve the temporal sequence for IL-1 stimulation of COX synthesis into transcription and translation phases by the use of selective inhibitors. When fibroblasts were incubated for 3-4 hr with IL-1, only a small increase (30-40%) in PGE_2 production was observed. Cellular COX activity at the end of this initial incubation was increased by only 50-100% in the IL-1-treated cells. However, following further incubation for 4 hr in the absence of IL-1, a dramatic 5-fold increase in COX activity is observed (Table 1). Inhibition of transcription with actinomycin D during the initial 4 hr blocked subsequent induction of COX activity, as well as [^{35}S]COX production (Fig. 4), whereas the presence of actinomycin D during the second incubation period (4-8 hr) did not affect COX induction or PGE_2 synthesis (Table 1). Addition of the translation inhibitor cycloheximide during the second incubation period produced total inhibition.

IL-1 Induction of COX Synthesis is Mediated via Activation of Protein Kinase C. Phorbol myristate acetate (PMA), a tumor promoter and potent protein kinase C (PKC) activator, was found to produce a significant, albeit modest, increase in COX activity (Table 2) and in the synthetic rate of newly formed ^{35}S-labeled enzyme (10). This PMA effect was dose-dependent in the 1-100 nM range and blocked by cycloheximide or actinomycin D if added together with PMA. Addition of PMA together with IL-1 produced a marked synergistic stimulation of COX induction (Table 2). We employed protein kinase inhibitors to evaluate the possible role of PKC in mediating IL-1 stimulation of COX. We used the PKC inhibitor H-7 and compared its effect to that of the non-PKC inhibitor HA1004. The results (Fig. 1) showed that H-7, but not HA1004, totally inhibited the stimulatory effect of IL-1 on COX activity and mass. Similar effects to those of H-7 were also observed with 25 nM staurosporine, a highly potent inhibitor of PKC. H-7 was found to exert its inhibition of COX when added during the initial 4 hr incubation

(presumed transcription phase) but to have no effect if added during the presumed translation phase (Fig. 1). Therefore, we conclude that the IL-1 signal transduction mechanism to induce COX synthesis involves a critical step in which activation of PKC is required.

TABLE 2. IL-1 Induction of Fibroblast Cyclooxygenase: Effect of PMA

Agent	Cyclooxygenase Activity Pg $PGE_2/\mu g$ protein/10 min
	58 ± 8*
IL-1 (1 unit/ml)	355 ± 36
PMA (10^{-7} M)	99 ± 16
IL-1 + PMA	765 ± 113

* Mean ± SEM (n=4)

Anti-inflammatory Glucocorticoids Inhibit COX Synthesis. Following the initial report by Pash and Bailey (11) on the apparent dexamethasone (DEX) blockade of COX synthesis in vascular smooth muscle cells, we carried out detailed studies on the effect of glucocorticoids on fibroblast COX. Addition of DEX (2 μM) throughout the entire transcription-translation sequence produced a marked inhibition of IL-1-stimulated COX activity (Fig. 2). In subsequent experiments, we found that the full inhibitory effect of the steroid was obtained when it was added only during the presumed translational period (i.e., 4-8 hr). DEX is a highly potent inhibitor of COX synthesis (>92% inhibition at 20 nM; IC_{50} of $\approx$1 nM) (10). Non-glucocorticoid steroids do not affect COX synthesis. The DEX-induced effect was completely reversed by actinomycin D (Fig. 3, panel A), suggesting that it involves the synthesis of one or more new proteins.

Can the stimulatory effect of IL-1 and the inhibitory effect of dexamethasone be demonstrated at the level of cellular mRNA? To answer this, we prepared total RNA from FB pretreated with IL-1 with or without DEX and used the RNA for *in vitro* translation experiments employing a rabbit reticulocyte lysate kit. The results of these studies (Fig. 3, Panel B) are in complete agreement with those obtained for ^{35}S-COX synthesized by intact cells (Fig. 3, Panel A). Thus both the stimulatory effect of IL-1 and the suppressing effect by DEX appears to be due to up-regulation or down-regulation, respectively, of COX mRNA.

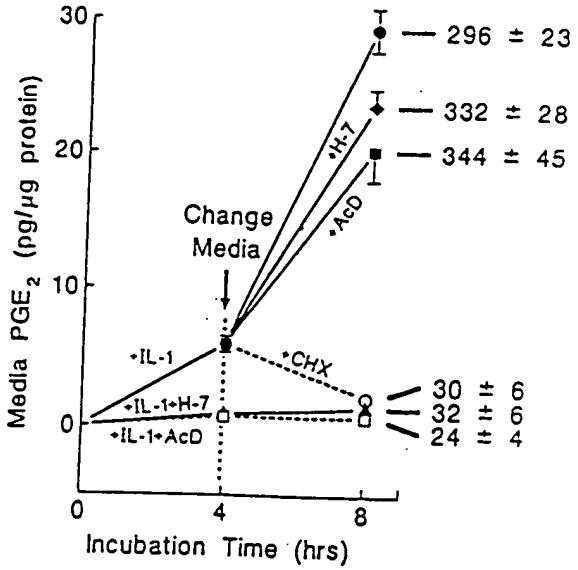

FIG. 1. PKC inhibitors block IL-1-induction of COX synthesis. Fibroblasts were initially incubated for 4 hrs with IL-1 (0.3 μ/ml) in the absence or presence of actinomycin (1 μM), H-7 (15 μM) or HA 1004 (15 μM). The cells were then washed and fresh DMEM media added with or without the same agents, as indicated in the figure, and the cells incubated for additional 4 hrs. PGE_2 released into the media is plotted on the Y axis and values for COX activity at the 8 hr time point are given for each sample. Modified figure from ref. 10.

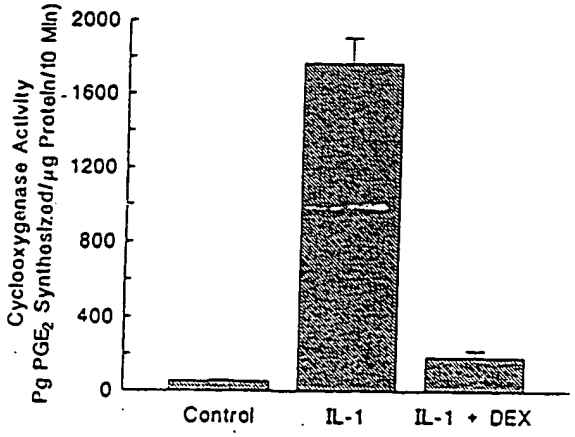

FIG. 2. Dexamethasone (DEX) inhibition of COX synthesis. Cells were first incubated for 4 hrs with either no DEX or IL-1 ("control"); with IL-1 (0.3 unit/ml) ("IL-1") or with both IL-1 and DEX (2 μM) ("IL-1 + DEX"). The cells were then washed with DMEM and incubated for 10 hrs without DEX ("control", "IL-1") or with DEX ("IL-1 + DEX") and COX activity of cell sonicate samples was then determined.

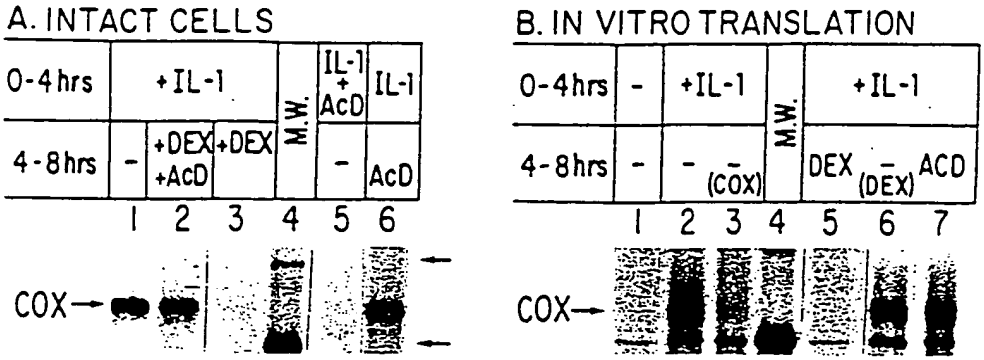

FIG. 3. IL-1 and DEX regulation of COX synthesis: In vitro translation experiments. Fibroblasts were incubated according to a two period protocol in the absence or presence of IL-1 (0.3 u/ml); DEX (40 nM), and actinomycin D (AcD, 1 μM). Some of the cells were then labelled with ^{35}S-methionine and cell sonicates then subjected to immunoprecipitation and SDS-PAGE electrophoresis (Panel A, from ref. 10). In parallel cell samples, total RNA was isolated by standard methods and used together with rabbit reticulocytes lysate kit for *in vitro* translation incubation (Panel B).

We have recently begun studies on the regulation of COX synthesis in monocytes/Mϕ. Studies by others have shown that bacterial lipopolysaccharide (LPS) can stimulate PGE_2 and TxB_2 production by blood monocytes and peritoneal Mϕ. In studies we performed, LPS dose-dependently (0.01-1 μg/ml) stimulated the COX activity and the rate of ^{35}S-COX synthesis. DEX inhibited monocytes COX activity but did not affect Tx-synthase activity (Table 3) or prostacyclin synthase (not shown).

The inhibitory effect of DEX on COX activity and thus prostanoid synthesis is novel and distinct from other inhibitory effects of DEX on eicosanoids production which are mediated very acylhydrolase(s) blockade. The relative contribution of the COX inhibition vs. acylhydrolase inhibition to the overall blockade of prostanoid generation by glucocorticoids under physiological and pathophysiological situations remains to be elucidated.

TABLE 3. DEX inhibits COX synthesis in human blood monocytes.*

Sample	Media PGE_2 pg/μg protein	COX Activity pg/min PGE_2/ μg protein	Media TxA_2 pg/μg protein	Tx-Synthase Activity pg TxB_2/μg protein/min
Control	8 ± 2	24 ± 6	30 ± 10	185 ± 24
LPS	255 ± 52	110 ± 12	2850 ± 180	149 ± 88
LPS + DEX	30 ± 4	23 ± 4	630 ± 65	205 ± 18

*Human blood monocytes fraction was allowed to adhere for 2 hrs in DME containing 1% FBS. Non-adherent cells were then removed and adhering cells incubated for 24 hrs with LPS in the absence or presence of DEX (40 nM). At the end of the incubation, COX activity was assayed by adding arachidonic acid (30 μM) plus BSA (1 mg/ml) for 10 min and determining PGE_2 produced. Tx synthase activity was assayed by incubating parallel samples with PGH_2 (5 μM) for 1 min and assaying for TxB_2 generated. Values are Mean ± SEM (n=3).

ACKNOWLEDGEMENT

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Celecoxib GD Searle & Co

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Current Opinion in Anti-inflammatory & Immunomodulatory Investigational Drugs 1999 1(2):100 -110

Celecoxib, a 1,5-diarylpyrazole, is an oral anti-inflammatory agent under development by Searle in collaboration with Pfizer as a potential treatment for rheumatoid arthritis (RA), osteoarthritis (OA) and pain. Celecoxib selectively inhibits inflammation-induced cyclooxygenase-2 (COX-2) activity [270568]. In December 1998, the compound was recommended for approval, in the US, for the treatment of OA and RA [309198]. It was approved in January 1999, in Brazil for the treatment of OA and RA, inflammation and pain [312280,312257] and launched in the US for RA and OA [301606,312280].

In August 1998, celecoxib received priority review from the FDA for the treatment of OA and RA, and pain management [295780]. The FDA may consider a specific indication for the relief of post-dental surgical pain, for celecoxib, rather than a broader acute pain indication [309200].

In February 1998, Searle entered into a definitive US agreement with Pfizer covering the co-promotion and development of celecoxib and its second generation compound [278450]. Under the terms of the agreement, Searle received an upfront payment of $85 million [279686]. In March 1998, this agreement was expanded to a worldwide development and commercial collaborative agreement, except for Japan where Yamanouchi and Searle have a similar agreement. The total upfront payment from Pfizer to Searle is now $100 million, with additional development and milestone payments also expected [282150].

Predictions for revenue range from US $650 million to $1 billion in the first year [300257]. Merrill Lynch predicts celecoxib will be the biggest product of 1999 given the popularity of a potent anti-inflammatory without the side-effects typical for a non-steroidal anti-inflammatory drug (NSAID). It also has the strongest sales rep backing ever seen by a new product during its launch with co-promotion agreements between Monsanto, Pfizer and American Home Products [301606].

Originator GD Searle & Co

Licensees Pfizer Inc, Yamanouchi Pharmaceutical Co Ltd

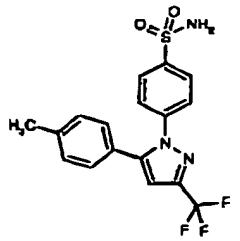
Status Launched

Indication Osteoarthritis, pain, inflammation, rheumatoid arthritis, colon tumor

Action Cyclooxygenase-2 inhibitor

Synonyms SC-58635, YM-74177, YM-177, Celebra, Celebrex

CAS Benzenesulfonamide, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]
Registry No(s): 184007-95-2



Synthesis and SAR

The full details of the synthesis of celecoxib have been reported [250139]. In this paper, the authors evaluated a series of sulfonamide-containing 1,5-diarylpyrazole derivatives for their ability to inhibit cyclooxygenase (COX)-1 and COX-2 *in vitro* and *in vivo*. Pharmacokinetics of various compounds were also assessed. These studies led to the identification of celecoxib as a lead compound.

The X-ray crystal structures of COX-2 and COX-1 have been compared. The active site of COX-2 differs from that of COX-1, in that it includes a 'side pocket' near the active site into which the Searle inhibitors bind [207339]. These compounds do not bind as well to COX-1. This detailed knowledge of the structures of COX-1 and COX-2 is being exploited by Searle in the design of second and third generation COX-2 inhibitors.

Pharmacology

Using insect cells transfected with human COX-1 and COX-2, Reddy and coworkers found that celecoxib inhibited the two enzymes with IC_{50} values of 13 and 0.04 mM, respectively [227187]. Thus, celecoxib exhibited 325-fold selectivity for inhibiting COX-2 over COX-1. Whilst selectivity for COX-2 over COX-1 *in vivo* has not been reported, celecoxib has been shown to reduce carrageenan-induced paw edema (ED_{50} = 7.1 mg/kg) and to inhibit pain in the Hargreaves hyperalgesia model (ED_{50} = 34.5 mg/kg) [250139]. In another study [226298], the ED_{50} for the blockade of COX-2 *in vivo*, in the rat, was 0.3 mg/kg, whilst the ED_{50} for reducing edema and hyperalgesia induced by a carrageenan injection into the paw was 10 mg/kg. It is not clear why the dose necessary for anti-inflammatory and analgesic effects was 33-fold greater than that required for inhibition of

COX-2. However, an earlier study with another Searle COX-2 inhibitor similarly showed that much greater doses (100-fold) of the drug were required to reduce inflammation and pain than were necessary to inhibit COX-2 activity *in vivo* [168282].

Celecoxib reduces the incidence of aberrant crypt foci in a rat model of colonic adenocarcinoma [227187]. These aberrant crypts are considered to be precancerous lesions. Celecoxib produced significant effects when added to the diet of rats at a concentration of 1500 ppm, but not when added at 150 ppm. Sulindac (Cell Pathways Inc), an NSAID, which has been suggested to reduce the incidence of colonic adenocarcinoma in humans, significantly reduced the number of aberrant crypt foci at a concentration of 320 ppm. While the authors of this study concluded that celecoxib produced its beneficial effects through selective inhibition of COX-2 activity, the data presented by Reddy *et al* suggest just the opposite. The lower concentration of celecoxib was selected because it would produce a plasma level of 0.5 μM. However, the authors report in the paper that maximal anti-inflammatory effects (presumably related to suppression of COX-2) were achieved with plasma concentrations of 0.3 μM. Thus the drug did not produce significant effects in this colonic cancer model when given at a dose sufficient to produce plasma levels almost double that required to inhibit COX-2. The concentration of celecoxib that significantly reduced the number of aberrant crypt foci was reported to produce plasma levels more than 10-fold greater than those necessary for inhibition of COX-2. Unfortunately, the authors did not present data on the inhibition of COX-1 and COX-2, *in vivo*.

Metabolism

No data are currently available.

Toxicity

Celecoxib did not induce gastric injury in rats at doses of up to 600 mg/kg/day [250139]. Single doses of up to 1200 mg were well-tolerated in volunteers [236664].

Clinical Development

Phase I

After a single dose of 100 mg of celecoxib in volunteers, the plasma levels at 1 h were 153 ± 115 ng/ml (mean +/- SD), while after a single 400 mg dose, the plasma levels 1 h later were 381 ± 319 ng/ml [240330]. Single doses of celecoxib from 1 to 1200 mg were reported to be safe and to have linear kinetics [236664]. Celecoxib has a half-life of 12 h and a T_{max} of 2 h [250139].

Six volunteers were given celecoxib at a dose of 400 mg daily for 6 days, after which time platelet aggregation was measured [250139]. Celecoxib exhibited no effect. In contrast, a single dose of aspirin (dose not specified) produced significant inhibition of platelet aggregation. The implication of this study is that after daily ingestion of celecoxib at 400 mg, no effect on COX-1 (platelet thromboxane synthesis) is detectable.

Groups of 32 volunteers each received placebo, celecoxib at 100 or 200 mg twice daily or naproxen (Elan Corp) at 500 mg twice daily [254590]. After 7 days, upper gastrointestinal endoscopy was performed and the extent of gastroduodenal damage was blindly scored. Naproxen caused gastric ulcers in 19% of the subjects, whilst neither dose of celecoxib caused ulcers. Erosions were seen in the stomach and duodenum following celecoxib administration, but the incidence did not differ significantly from that seen in the placebo group and was significantly less than that seen in the naproxen group. It is not clear if the doses of celecoxib used were as effective as the dose of naproxen, in terms of the reduction of inflammation or pain.

Phase II

In a study of dental pain (third molar extractions; 200 patients), celecoxib given at doses of 100 or 400 mg produced relief of pain within 45 min, with the duration of pain relief lasting for more than 4 h [240330]. The effects of celecoxib at 100 and 400 mg were equivalent, and were also comparable to those achieved with aspirin at 650 mg.

In another study, involving 293 people with OA of the knee, who had experienced a flare, celecoxib (40, 100 or 200 mg) was compared to placebo [229695,309510]. The drugs (or placebo) were administered twice daily for 2 weeks. Various efficacy parameters were monitored (including both patient and physician assessments). Celecoxib was well-tolerated and all three doses showed significant effects on some of the parameters of pain relief. However, the magnitude of difference from the placebo response was often quite small, and there appeared to be a limit to the efficacy that could be achieved with this drug. Almost 50% of the patients treated with the highest dose of celecoxib were treatment failures (ie, did not show improvement). Moreover, for some parameters the effects were not dose-dependent, eg, in the case of the 'OA severity index', only the lowest dose of celecoxib produced a significant effect relative to placebo. As this study did not include a comparative drug (eg, a standard NSAID), it is difficult to assess the significance of the magnitude of effects observed with celecoxib on many of the measured parameters of inflammation and pain.

Phase III

In a pivotal 12-week phase III study involving 1149 RA patients in active disease (flared) state, celecoxib (100, 200 and 400 mg bid) was as effective as 500 mg bid naproxen, and superior to placebo, in relieving joint tenderness, pain and swelling [304918].

Another 12-week study involving 1004 patients with OA demonstrated that celecoxib (100 or 200 mg bid) was again as effective as 500 mg naproxen bid and better than placebo in relieving the symptoms of OA [304918].

Celecoxib does not interact with methotrexate, lithium, glyburide or warfarin. Celecoxib (600 mg bid) was compared with naproxen (500 mg) and placebo, in a platelet study. In contrast to naproxen, celecoxib produced no effect on platelet aggregation or bleeding time [286094].

In a phase III endoscopy trial with celecoxib (100, 200 and 400 mg bid), ulcers were observed in 5% of patients, an effect which was not significantly different from the placebo-treated group [286094].

Current Opinion

An increased understanding of the structures of COX-2 and COX-1 has permitted rational design of drugs with selective inhibitory actions on these two enzymes. Celecoxib has 325-fold selectivity for COX-2 over COX-1 *in vitro*. It is likely to be the first selective COX-2 inhibitor to reach the marketplace, followed shortly by Vioxx (rofecoxib, Merck). There is some evidence that celecoxib does not affect COX-1 activity at doses that are effective in reducing pain. Whether or not the degree of selectivity for COX-2 *in vitro* will occur *in vivo* remains to be seen.

Celecoxib was superior to placebo in clinical trials in which relief of pain and inflammation were assessed. The biggest question remaining about celecoxib and the other selective COX-2 inhibitors concerns efficacy. It needs to be determined whether these drugs can reduce inflammation and pain as effectively as agents that have mixed COX-1 and COX-2 activity. Accordingly, comparisons to existing NSAIDs are eagerly awaited.

In terms of toxicity, celecoxib appears to produce much less gastroduodenal injury than standard NSAIDs, such as naproxen. Given concerns that selective COX-2 inhibition will not achieve anti-inflammatory or analgesic effects comparable to those which can be achieved with mixed COX-1/COX-2 inhibitors, it is important that toxicity studies are performed in which equieffective doses of COX-2 inhibitors and non-selective COX inhibitors are compared. A potential concern is the use of celecoxib and other selective COX-2 inhibitors in patients with pre-existing ulcers or inflammation. In several animal studies, selective COX-2 inhibitors interfered with healing of ulcers and to exacerbate inflammation [243988,257140]. As the majority of patients with NSAID-related gastric ulcers do not experience symptoms that would alert them to their condition, there is potential danger in the widespread use of an agent that might exacerbate or delay the healing of ulcers in a population with a high incidence of 'silent' gastroduodenal ulceration.

Claims that celecoxib reduces the incidence of colonic adenocarcinoma through selective blockade of COX-2 should be regarded with some degree of skepticism, given the lack of strong evidence to support this claim. The existing data suggest that the beneficial effects of celecoxib in a rat model were due to non-specific effects of this drug.

Licensing

American Home Products Corp

Co-promotion agreement with Pfizer and Monsanto [301606].

Pfizer Inc

Worldwide agreement, excluding Japan, for the co-promotion and development of celecoxib [278450].

Yamanouchi Pharmaceutical Co Ltd

Under the terms of this agreement, Yamanouchi will lead the development of the compound in Japan and will collaborate with Searle to support co-registration by both companies. Yamanouchi will pay a one-time licensing fee, make milestone payments, pay royalties and purchase the compound from Searle [275105].

National Cancer Institute

In collaboration for trials in familial adenomatous polyposis [325063].

Development History

DEVELOPER	COUNTRY	STATUS	INDICATION	DATE	REFERENCE
GD Searle & Co	US	L	Rheumatoid arthritis	05-FEB-99	312280
GD Searle & Co	US	L	Osteoarthritis	05-FEB-99	312280
Pfizer Inc	US	L	Rheumatoid arthritis	05-FEB-99	316041
Pfizer Inc	US	L	Osteoarthritis	05-FEB-99	316041
American Home Products Corp	US	L	Rheumatoid arthritis	01-JAN-99	301606
American Home Products Corp	US	L	Osteoarthritis	01-JAN-99	301606
GD Searle & Co	Brazil	R	Inflammation	25-JAN-99	312257
GD Searle & Co	Brazil	R	Pain	25-JAN-99	312257
Pfizer Inc	US	PR	Osteoarthritis	15-OCT-98	295780
Pfizer Inc	US	PR	Rheumatoid arthritis	15-OCT-98	295780

Development History (continued)

DEVELOPER	COUNTRY	STATUS	INDICATION	DATE	REF
GD Searle & Co	Western Europe	PR	Rheumatoid arthritis	15-OCT-98	295780
GD Searle & Co	Western Europe	PR	Pain	15-OCT-98	295780
GD Searle & Co	Western Europe	PR	Osteoarthritis	15-OCT-98	295780
GD Searle & Co	US	C3	Inflammation	25-NOV-96	226298
GD Searle & Co	Western Europe	C3	Inflammation	25-NOV-96	226298
Yamanouchi Pharmaceutical Co Ltd	Japan	C2	Rheumatoid arthritis	01-NOV-96	249525
GD Searle & Co	US	C2	Pain	18-APR-96	205479
Pfizer Inc	US	C2	Pain	18-APR-96	205479
Yamanouchi Pharmaceutical Co Ltd	Japan	C2	Osteoarthritis	01-NOV-96	249525
Yamanouchi Pharmaceutical Co Ltd	Japan	C1	Inflammation	18-APR-96	205479
Pfizer Inc	US	DR	Colon tumor	16-DEC-98	291337
Yamanouchi Pharmaceutical Co Ltd	Japan	DR	Colon tumor	16-DEC-98	291337
GD Searle & Co	Western Europe	DR	Colon tumor	29-DEC-98	291337

Literature classifications

Key references relating to the drug are classified according to a set of standard headings to provide a quick guide to the bibliography. These headings are as follows:

Chemistry: References which discuss synthesis and structure-activity relationships.

Biology: References which disclose aspects of the drug's pharmacology in animal models.

Clinical: Reports of clinical phase studies in volunteers providing, where available, data on the following: whether the experiment is placebo-controlled or double- or single-blind; number of patients; dosage.

Chemistry

STUDY TYPE	RESULT	REFERENCE
Synthesis and SAR	Full synthetic details plus analysis of the effects of structural changes on COX-1 and COX-2 activity and on metabolic parameters.	250139

Biology

STUDY TYPE	EFFECT STUDIED	EXPERIMENTAL MODEL	RESULT	REFERENCE
In vitro	COX-1/COX-2 selectivity.	Insect cells transfected with human COX-1 and COX-2.	Celecoxib had 325-fold selectivity for COX-2 over COX-1.	227187
In vivo	Anti-inflammatory effects.	Carageenan-induced paw edema, rat.	Celecoxib reduced paw edema, ED_{50} = 7.1 mg/kg.	250139
In vivo	Antihyperalgesic effects.	Hargreaves hyperalgesia model, rat.	Celecoxib inhibited hyperalgesia, ED_{50} = 34.5 mg/kg.	250139
In vivo	Gastric injury.	Rat.	Celecoxib did not induce gastric injury at doses of up to 500 mg/kg/day.	250139
In vivo	Inhibition of PGE_2 synthesis in inflammatory tissue.	Air pouch plus carageenan, rat.	Celecoxib inhibited PGE_2 synthesis, ED_{50} = 0.3 mg/kg po.	226298
In vivo	Inhibition of PGE_2 synthesis in gastric tissue.	Rat.	Celecoxib inhibited PGE_2 synthesis, ED_{50} = 10 mg/kg po.	226298

Clinical

EFFECT STUDIED	EXPERIMENTAL MODEL	RESULT	REFERENCE
Toxicity	Phase I trial, healthy volunteers	Single doses of celecoxib of up to 1200 mg were well-tolerated and had linear kinetics	236664
Gastroduodenal damage	Phase I trial: Celecoxib (100 or 200 mg bid), naproxen (500 mg bid) or placebo administered to healthy volunteers	After 7 days, gastrointestinal endoscopy revealed that neither dose of celecoxib caused gastric ulceration or naproxen which caused ulceration in 19% of subjects	254590
Platelet aggregation	Phase I trial: Six volunteers given 400 mg celecoxib for 8 days	Celecoxib had no effect on platelet aggregation, unlike aspirin which inhibited platelet aggregation	250139
Analgesic efficacy	Phase II trial. Single dose of 100 or 400 mg in a model of post-extraction dental pain	At least as effective as 650 mg aspirin, time to onset of analgesia = 45 min	240330
Pain relief	Phase II trial in 293 subjects with OA of the knee	Celecoxib produced some pain relief. However, as no comparative NSAID was used in this study it is difficult to fully assess the significance of the effects of celecoxib on many of the measured parameters of inflammation and pain	229695, 309510
Relief of joint tenderness, pain and swelling	12-week, phase III study in 1194 active (flared state) RA patients	Celecoxib (100, 200 and 400 mg bid) was as effective as 500 mg naproxen and superior to placebo	304918
Symptomatic relief of OA	12-Week, phase III study in 1004 OA patients	Celecoxib (100 and 200 mg bid) was as effective as 500 mg naproxen and superior to placebo	304918
Gastroduodenal ulceration	Phase III trial	Ulcers were observed in 5% of patients treated with celecoxib (100, 200 and 400 mg bid) which was not significantly different of placebo	286094

Associated patent WO-09515316

Title Substituted pyrazolyl benzenesulfonamides for the treatment of inflammation.

Assignee GD Searle & Co

Publication WO-09515316 08-JUN-95

Priority US-00160594 30-NOV-93

Inventors Talley JJ, Penning TD, Collins PW

Abstract

Novel 3,4,5-tri-substituted-1-phenyl-sulfoxyamine-substituted pyrazole derivatives are claimed, which are stated to selectively inhibit COX-2. They are potentially useful for the treatment of inflammation and inflammation-associated disorders and are specifically claimed for the treatment of arthritis, pain and fever. A rat carrageenan footpad edema test and a rat carrageenan-induced analgesia test were performed. An *in vitro* assay of COX-1 and COX-2 activity is also described. Eight reaction schemes and 262 synthetic examples are presented. Over 100 compounds are specifically claimed including the specified compound, ethyl 1-[4-(amino-sulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazole-3-carboxylate.

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